REMARKS AND RESPONSE TO OFFICE ACTION

After entry of this paper claims 15-20 and 22-24 are pending.

Antecedent basis for claimed subject matter

The Office objected to the specification as failing to provide proper antecedent basis the phrase "cyclodextrin inclusion complex" as required at 37 C.F.R. § 1.75(d)(1). Support for inclusion complexes is at example 11, which provides a protocol to solubilize 17α-AED by making inclusion complexes with β-cyclodextrin. Such solutions would contain inclusion complexes, as would have been understood by one of ordinary skill in the art at the time the application was filed. Cyclodextrins were used to solubilize water-insoluble drugs, including steroids, see, e.g., U.S. patent Nos. 5,824,668 and 4,383,992, both newly cited. Also, amended claim 19 recites cyclodextrin as a component of the claimed composition and the objection should now be moot. Applicant respectfully requests reconsideration and withdrawal of the objection, in view of the disclosure, including example 11.

35 U.S.C. § 112, first paragraph

The Office objected to the specification and rejected claims 15-20 and 22-24 as enabled for treating human breast cancer, but allegedly not enabled for any other tumor type. However, the Office also stated that the objection would be overcome if the claims were amended to recite a "composition of matter comprising a tumor inhibiting effective amount. . . ". For reasons described below, Applicant respectfully requests reconsideration and withdrawal of the rejection.

As an initial matter, Applicant's file indicates that the preamble of claims 15 and 19, the only independent claims in the application when the Office issued this Office action, contained the phrase "a composition of matter for inhibiting tumors comprising a tumor inhibiting effective amount of . . . ". It thus appears that the phrase the Office suggested for the claims was already present.

The following comments are presented in the event that the phrase the Office suggested to render the claims enabled is considered insufficient by the Office to enable the claims.

To establish and maintain a rejection under 35 U.S.C. §112, first paragraph, the Office must provide logical reasoning to support its position. The Office must "explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *In re Marzocchi and Horton*, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971). The Office must advance "substantive reasons why the instant specification is non-enabling." "Mere broad generalizations and allegations are insufficient for holding of non-enablement." *Ex parte Goeddel* 5 U.S.P.Q. 2d 1449 (B.P.A.I. 1987). The first paragraph of 35 U.S.C. § 112 requires nothing more than objective enablement. *In Re Vaeck* 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991), *Atlas Powder Co. v. E.I. Du Pont De Nemours & Co.* 224 U.S.P.Q. 409 (Fed. Cir. 1984). It is irrelevant whether objective enablement is based on working examples or on broad terminology. *In Re Vaeck*, supra, *Atlas Powder Co.*, supra. To meet the requirement under the first paragraph of § 112, the specification, when filed, must enable one skilled in the particular art to use the invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988), *Ex parte Forman* 230 U.S.P.Q. 546 (B.P.A.I. 1986). In addition, even if some of the claimed embodiments were inoperative, the claims are not necessarily invalid. "It is not a function of the claims to specifically exclude . . . possible inoperative substances . . . ." *Atlas Powder Co.*, supra, *In re Dinh-Nguyen*, 492 F.2d 856 (C.C.P.A. 1974).

The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. *In re Wands, supra*. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a

reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *Ex parte Jackson, et al.*, 217 U.S.P.Q. 804 (B. P. A. I. 1982), *In re Ranier, et al.*, 146 U.S.P.Q. 218 (C.C.P.A. 1965). As explained below, Applicant respectfully submits that the specification enabled the claimed subject matter.

Applicant notes that the claims the Office examined were composition of matter claims and the present revised claims are composition of matter claims. In the Office action, the Office stated that the use of treating the human breast cancer cells disclosed in the application was enabled. Applicant also notes that the Office apparently overlooked data in the application showing activity against additional cancers. Specifically, 17α-AED was shown at example 8 to be active against the P388D1 lymphocyte tumor cell line and at example 9 against the murine RAW 264.7 macrophage myeloma cell line. Also, data showing activity against the human HL-60 myelocytic leukemia cells is at P.N. Huynh and R.M. Loria, *J. Leukocyte Biol.* 62:258-267 1997, of record and activity against estrogen receptor negative human MDA-MB231 breast cancer cells is at P.N. Huynh et al., *Cancer Detection and Prevention* 24:435-444 2000, newly cited.

Collectively, this is objective evidence that various cancers are all susceptible to treatment, which is sufficient to enable at least those uses. Because of this, the claims do not need to enable the treatment of any other cancer. *In re Atlas Powder Co., supra*, *In re Dinh-Nguyen, supra*. Instead, the claims must enable the preparation of the claimed compositions. The Office's rationale for the rejection centers on enablement of cancer treatment methods. The claims in this application do not recite treating any cancer. Applicant does need to enable the claimed compositions, but not treatment methods. Applicant notes that the issued parent patent, U.S. No. 5,912,240, of record, claims methods to inhibit sensitive tumor cells. This subject matter is presumed to be enabled and it is thus evidence that the compositions are enabled since they would be employed in the practice of the methods that the '240 patent claims. Absent further clarification of the rejection by the Office, Applicant is not aware of

what additional specific teaching would be needed to avoid undue experimentation, particularly where extensive experimentation may be permitted. *In re Jackson*, *supra*, *In re Ranier, supra*. To maintain the rejection, the Office must explain why the claimed compositions could not be made or used in the enabled methods of use.

Applicant respectfully requests reconsideration and withdrawal of the rejection.

35 U.S.C. § 112, second paragraph

The Office rejected all pending claims for unclear language, including the use of the words "may", "including" and "(including benzyl)" instead of standard claim language for chemical compounds. Applicant has amended the claims to remove all of these informalities and the rejection should now be moot.

35 U.S.C. § 103(a)

The Office rejected claims 15-20 as allegedly unpatentable over U.S. patent No. 4,898,694 (Schwartz and Lewbart, hereafter the '694 patent), of record and claims 22-24 as allegedly unpatentable over the '694 patent in view of U.S. patent No. 5,206,008 (Loria, hereafter the '008 patent). Applicant respectfully traverses the rejections.

To establish and maintain a rejection under 35 U.S.C. § 103(a), the Office must show that the cited references must contain a suggestion or motivation to select the claimed subject matter. *In re Dillon*, 16 U.S.P.Q. 2D 1897 (Fed. Cir. 1990). All evidence of the properties of the claimed compositions and the prior art must be considered in determining the ultimate question of patentability. *In re Dillon, supra.* Hindsight reconstruction cannot be used to pick and choose among isolated disclosures in the prior art to arrive at a conclusion of obviousness. *In re Dembiczak*, 50 U.S.P.Q. 2D 1614 (Fed. Cir. 1999), *In re Fine* 5 U.S.P.Q. 2D 1596 (Fed. Cir. 1988).

The Office asserted that claims 15-20 would have been obvious over the disclosure at column 4, line 55 through column 6, line 23 and column 74, lines 18-19 in the '694 patent because when the R^5 variable group is hydroxy or alkoxy and the other substituents are hydrogen, the presently claimed compositions would have been obvious. Review of that subject matter shows that '694 patent broadly discloses a steroid nucleus with 16 or more variable groups, most of which can be a large number of individual species, e.g., hydrogen, hydroxyl, halogen, alkyl and alkoxy. A review of the '694 patent shows there is insufficient disclosure to provide written description to claim or describe either 17α-AED or ether derivatives thereof. In general, the '694 patent directs one to select compounds that contain only hydrogen or hydrogen and alkyl moieties at the 3-position, see e.g., column 8, lines 9-11 and the claims. It is thus fair to conclude that the '694 patent thus does not expressly or inherently describe the 17α-AED compound or ethers thereof, since there is insufficient written description to support the species or the genus. In view of this, it is apparent that hindsight reconstruction was used to pick the compositions that Applicant now claims. Such use of hindsight is impermissible. *In re Dembiczak, supra*. Because of this, Applicant respectfully submits that the '694 patent contains no suggestion to select the claimed compositions.

Also, it is clear that the '694 patent does not provide a reasonable expectation of success. At column 73, lines 3-17, the '694 patent states that the compounds act by inhibiting glucose-6-phosphate dehydrogenase. The data in the table at column 73 shows that significant inhibition of the glucose-6-phosphate dehydrogenase enzyme requires concentrations of 10 μM. The compounds in '694 at 1 μM did not significantly inhibit the enzyme. By contrast, Applicant's data at, e.g., examples 1 and 9 shows that 17α-AED is active at 12.5 nanomolar, 50 nanomolar and 100 nanomolar concentrations. These concentrations are much lower than the 10 μM concentration the '694 patent shows is necessary to significantly inhibit the enzyme with steroids that have a hydroxyl group at the 17-position. Other work has shown similar degrees of

inhibition of glucose-6-phosphate dehydrogenase by related steroids, but with a preference for a steroids that have a 17-keto group instead of a 17-hydroxyl or ester. G.W. Oertel and P. Benes, *J. Steroid Biochem.* 3:493-496 1972, newly cited. It is clear that 17α-AED at 100 nanomolar concentrations or less would not have been expected to be an effective anti-cancer agent. Applicant's data is clear objective evidence of unexpected activity, since anticancer activity observed with 17α-AED can be obtained at much lower concentrations than with the compounds described in the '694 patent at column 73. Also, as noted in Applicant's application, the compounds act by inducing programmed cell death, which is not taught or suggested by the '694 patent.

Similarly, claims 22-24 are patentable over the '694 patent in view of the '008 patent, since the '008 patent does not alter the evidence of unexpected activity. At page 7, lines 11-13 of the present application, the β-enantiomer (17β-AED) at 100 nanomolar did not inhibit tumor ZR-75-1 cell proliferation, while 17α-AED at 100 nanomolar did inhibit ZR-75-1 cells. This evidence shows that the 17α enantiomer is much more potent than the 17β enantiomer. Applicant notes that the compounds described in the '694 patent at column 73, lines 10-17 are both 17β-hydroxyl compounds that do not contain either hydroxyl or alkoxy at the 3-position. These two compounds are representative of the preferred compounds in the '694 patent.

Conclusion

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the rejection. Applicants' representative can be reached at the number given below if the Office has any questions or would like to address any other matters that may arise.

Respectfully submitted,

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